BMT for acquired aplastic anaemia in adults

Judith Marsh
The Bone Marrow Failure Syndromes

RBDS – Ribosomal Dysgenesis syndromes
DC – Dyskeratosis congenita
FA – Fanconi Anaemia
AA – Aplastic Anaemia
PNH – Paroxysmal Nocturnal Haemoglobinuria
LGL – Large Granular Lymphocytosis

Adapted from N. Young, G. Mufti

Immune mediated Aplastic Anaemia

Marsh, Kulasekararaj, Mufti
Can one predict response to ATG at diagnosis?

### No. T-regs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Predictive?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>√</td>
</tr>
<tr>
<td>Disease severity</td>
<td>√</td>
</tr>
<tr>
<td>Reticulocyte count &gt; 25x10⁹/l</td>
<td>√</td>
</tr>
<tr>
<td>Lymphocyte count &gt; 1x10⁹/l</td>
<td>√</td>
</tr>
<tr>
<td>PNH clone</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Cytogenetics eg +8, -7</td>
<td>√</td>
</tr>
<tr>
<td>HLADR15+</td>
<td>X</td>
</tr>
<tr>
<td>Telomere length</td>
<td>X but.........</td>
</tr>
<tr>
<td>Future molecular markers</td>
<td>(√) ?</td>
</tr>
<tr>
<td>CD4+ T-cell subsets</td>
<td>(√) ?</td>
</tr>
</tbody>
</table>


Scheinberg. JAMA. 2010;304:1358
Algorithm for first line treatment of SAA

- **Age of patient**
  - ≤ 50yr
  - > 50yr

  - **HLA id sibling donor**
    - YES
      - HLA matched sibling HSCT
    - NO
      - Horse ATG (ATGAM) with CSA
        - Assess response at 3-4 months

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>HSCT</th>
<th>Total HSCT</th>
<th>IST 1st therapy</th>
<th>IST total therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>11,993</td>
<td>9,539</td>
<td>10,507</td>
<td>3,777</td>
<td>4,929</td>
</tr>
</tbody>
</table>

**Special Issue:** Treatment and Hematopoietic Stem Cell Transplantation in Aplastic Anemia
J Passweg and M Aljurf on behalf of the EBMT SAAWP
BMT 48, Issue 2 (February 2013)
HLA identical siblings 1999-2009: 10 yr OS stratified according to age

Bacigalupo, EBMT  SAAWP database 2012
Matched sibling HSCT: Cyclophosphamide 200mg/kg, ATG, ciclosporin + methotrexate

![Graph showing survival rates and GvHD percentages.]

- CY 200; n=1244, survival: 80%
- Other conditioning; n=642, survival: 72%
- ATG in conditioning; n=747, survival: 84%
- No ATG in conditioning; n=1139, survival: 74%

**Acute and chronic GvHD**

- <114 days from diagnosis; n=941, 84%
- ≥114 days from diagnosis; n=945, 72%

**P-values:**
- 0.0004
- 0.0004
- 0.0001
- 0.0004

**Percentage of patients:**

- II-IV
- III-IV
- cGvHD
- ext cGvHD
Matched sibling HSCT age > 40yr

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>N=1307</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>717</td>
</tr>
<tr>
<td>20-40</td>
<td>506</td>
</tr>
<tr>
<td>&gt;40</td>
<td>84</td>
</tr>
</tbody>
</table>

Gupta et al. Haematologica 2010; 95: 2119

Improved outcome of patients older than 30 years receiving HLA-identical sibling hematopoietic stem cell transplantation for severe acquired aplastic anemia using fludarabine-based conditioning: a comparison with conventional conditioning regimen

Maury et al. Haematologica 2009; 94:1312

- Fludarabine 30mg/m² x 4
- CY 300mg/m² x 4
- ATG
- CSA + MTX
What are the goals of HSCT in severe aplastic anaemia?

| Minimal toxicity from conditioning regimen | • Irradiation not indicated in MSD, and may not be needed for MUD  
| • Can avoid methotrexate when use alemtuzumab instead of ATG |
| Sustained haematological engraftment | • Graft failure (primary or late) in 10% MSD and 15-20% MUD  
| Full donor myeloid chimerism | • HLA alloimmunisation still a high risk  
| Stable mixed T-cell chimerism? | • Mixed T-cell chimerism is common and associated with absence of chronic GVHD (? state of tolerance)  
| Absence of any chronic GVHD | • Consider using alemtuzumab instead of ATG  
| Minimal long term complications | • Avoid irradiation and chronic GVHD  
|  | • Minimal use of prednisolone with prior ATG |
When is unrelated donor BMT indicated?
Algorithm for first line treatment of SAA

- **Age of patient**
  - ≤ 50yr
    - HLA id sibling donor
      - YES: HLA matched sibling HSCT
      - NO: Horse ATG (ATGAM) with CSA
        - Assess response at 3-4 months
        - No response
  - > 50yr
    - Unrelated donor HSCT

Improved survival after UDHSCT 1990-2005

Possible reasons?

1. High resolution HLA typing
2. Improved conditioning regimens:
   - Fludarabine, low dose TBI, alemtuzumab
3. Earlier time to transplant
4. Better supportive care
Fludarabine, cyclophosphamide, ATG (FCATG) with or without TBI 2Gy for UD HSCT

Patients transplanted 1998-2008

<table>
<thead>
<tr>
<th></th>
<th>FCATG (n = 52)</th>
<th>FCATG-TBI 2Gy (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med age</td>
<td>13 (3-51)</td>
<td>27 (7-53)</td>
</tr>
<tr>
<td>Rejection</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>cGVHD</td>
<td>9, ext. in 1 (27%)</td>
<td>14, ext. in 4 (50%)</td>
</tr>
<tr>
<td>P 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBVPTLD</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Bacigalupo et al, Haematologica 2010;95:976
UD HSCT in SAA

Is irradiation necessary?
How to reduce chronic GVHD?
Is irradiation necessary?

- Lee et al. BMT 2005; 35: 755
  N = 13; CY+ATG (9), CY+Flud (2), CY+ATG+Flud (2).
  All engrafted, acute GVHD III-IV 23%, extensive chronic GVHD 31%, 10/13 alive

- Kang et al. BBMT 2010; 16: 1582
  N = 28; CY 50mg/kg x 1, Flud, ATG
  All engrafted, acute GVHD III-IV 11%, extensive chronic GVHD 17%
  High TRM:TTP (2), pneumonia (1), MI (1), PTLD (3), GVHD (2), OS 68%
Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anemia

Judith C. Marsh,1 Vikas Gupta,2 ZiYi Lim,1 Aloysius Y. Ho,1 Robin Ireland,1 Janet Hayden,1 Victoria Potter,1 Mickey B. Koh,3 M. S. Islam,3 Nigel Russell,4 David I. Marks,5 *Ghulam J. Mutfi,1 and *Antonio Pagliuca1

**FCC conditioning regimen**

Fludarabine 30mg/m2 x 4  
Cyclophosphamide 300mg/m2 x 4  
Alemtuzumab 60mg (40-100)

Ciclosporin day -1 to 12 months

<table>
<thead>
<tr>
<th>Patients</th>
<th>N = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y) no. &gt; 50y</td>
<td>38 (8-62) 12</td>
</tr>
<tr>
<td>Median FU (range)</td>
<td>18mo (2-113)</td>
</tr>
<tr>
<td>Donor type</td>
<td>21 29</td>
</tr>
<tr>
<td>Sibling</td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td></td>
</tr>
<tr>
<td>Transplant period</td>
<td>6 44</td>
</tr>
<tr>
<td>1999-2004</td>
<td></td>
</tr>
<tr>
<td>2005-2010</td>
<td></td>
</tr>
<tr>
<td>Stem cell source</td>
<td>24/7/14/5</td>
</tr>
<tr>
<td>BM/G-BM/PBSC/PBSC+BM</td>
<td></td>
</tr>
<tr>
<td>Median interval Dx-HSCT (mo)</td>
<td>6 (2-252) 10 (4-137)</td>
</tr>
<tr>
<td>Sibling</td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td></td>
</tr>
</tbody>
</table>

Marsh et al. Blood 2011; 118: 2351
Alemtuzumab in HSCT for SAA

MSD vs MUD
- 95%
- 83%

Age < 50 yr
- 87%
- 73%

Co-morbidity score
- 0-1
- > 2

Acute GVHD
13.5% (16.5% CI at 1yr)

Chronic GVHD
4% (7% CI at 1yr)

PB chimerism

Marsh et al. Blood 2011; 118: 2351
Stem cell source: unrelated donor HSCT for SAA

- More acute GVHD with PB
- No increase in chronic GVHD after adjusting for age

BM 76% (n = 225)
PB 61% (n = 71)

P = 0.04

MUD HSCT, Eapen et al. CIBMTR
Blood 2011; 118:2618
Is alemtuzumab better than ATG for conditioning in SAA?
National, retrospective, multi-center comparison of Alemtuzumab- versus ATG-based conditioning regimens in HSCT for severe aplastic anemia (SAA): a study from the British Society for Blood and Marrow Transplantation (BSBMT) (CTCR 09-03)


- Transplants performed 1999-2009
- 22 centres
- First allograft for acquired SAA
- Median follow up: 38 mo (3-125)
- Median age: 20yr (1.5-67.5)
Patients

N = 155

MSD (87) + other related (6)  MUD (60) + mis-matched UD (2)

ATG (43 + 5)  Alemtuzumab (44 + 1)

ATG (7)  Alemtuzumab (55)

PBSC (n= 9)  BM (n= 37, 2 BM+PB)  PBSC (n= 9)  BM (n= 30, 6 BM+PB)  PBSC (n= 5)  BM (n= 2)  PBSC (n= 19)  BM (n= 36)
## Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Alemtuzumab (n=100)</th>
<th>ATG (n=55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow up (mo)</strong></td>
<td>38 (3-125)</td>
<td>62 (4-121)</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Engraftment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (9%)</td>
<td>6 (11%)</td>
<td>0.778</td>
</tr>
<tr>
<td>Yes</td>
<td>91 (91%)</td>
<td>48 (89%)</td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophil recovery (days)</strong></td>
<td>19 (10-89)</td>
<td>21 (12-34)</td>
<td>0.391</td>
</tr>
<tr>
<td><strong>Platelet recovery (days)</strong></td>
<td>20 (0-275)</td>
<td>21 (3-47)</td>
<td>0.631</td>
</tr>
<tr>
<td><strong>Chimerism @100d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete donor</td>
<td>44 (58%)</td>
<td>21 (66%)</td>
<td>0.721</td>
</tr>
<tr>
<td>Mixed</td>
<td>30 (39%)</td>
<td>10 (31%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Chimerism @ last FU</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete donor</td>
<td>37 (54%)</td>
<td>20 (71%)</td>
<td>0.237</td>
</tr>
<tr>
<td>Mixed</td>
<td>30 (43%)</td>
<td>8 (29%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68 (71%)</td>
<td>42 (76%)</td>
<td>0.694</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (29%)</td>
<td>13 (23%)</td>
<td></td>
</tr>
<tr>
<td>Grade I-II</td>
<td>25 (89%)</td>
<td>9 (69%)</td>
<td></td>
</tr>
<tr>
<td>Grade III-IV</td>
<td>3 (11%)</td>
<td>4 (31%)</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78 (89%)</td>
<td>37 (76%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (11%)</td>
<td>12 (24%)</td>
<td></td>
</tr>
<tr>
<td><strong>Limited/extensive</strong></td>
<td>7/3</td>
<td>9/3</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>for</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>extensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cGVHD</td>
</tr>
</tbody>
</table>
Overall survival: Alemtuzumab vs ATG

All patients

Matched siblings

Unrelated donors

P = 0.11

P = 0.562

P = 0.026
Conclusions from BSBMT study

• Confirms excellent outcomes after HSCT for SAA
• 5 yr OS of 88% for UD HSCT using alemtuzumab, without using irradiation
• No difference in OS for MUD and MSD HSCT in children
• Lower risk of chronic GVHD, and less grade III/IV acute GVHD with alemtuzumab
• For whole group, better OS using BM compared to PB
• Larger EBMT observational study on alemtuzumab vs ATG is in progress (Dr Sujith Samarasinghe)
What is the role of HSCT in refractory SAA, in the absence of a BM donor?
What does refractory SAA really mean?

• Failure to respond to 1st course of ATG at 6 months (Scheinberg and Young, Blood 2012)
• Is the diagnosis still AA and not hypoMDS?
• Does the patient have constitutional bone marrow failure?
• Is there stem cell exhaustion? Conversely, has there been inadequate immunosuppressive therapy?
• Time to re-evaluate the patient

Additional steps:
• Discussions on transplant and non-transplant options
• Enrol in clinical trial whenever possible
• Continue best supportive care
The impact of best supportive care in non-responders to immunosuppressive therapy

(HSCT censored)

Management of refractory AA patients

Refractory Aplastic Anemia
Persistence of severe cytopenia(s) at 6 months after one course of IST (ATG + CSA)

Availability of suitably matched donor

Yes

HSCT
Matched sib (>40-50yr) or unrelated donor

No

No response at 6 months

Repeat course of IST 2^{ND} ATG + CSA

Or

Alternate donor HSCT
- Haploidentical
- Umbilical cord

Alternate agents
- Alemtuzumab
- Trial of androgens
- Eltrombopag
- Experimental therapy in clinical trials

Predictors of nonresponse to IST
- older age
- low absolute reticulocyte count
- low lymphocyte count
- disease severity

• exclude hypocellular MDS
• exclude constitutional BMF
• continue best supportive care

Marsh and Kulasekararaj, 2013, submitted
Alternative donor HSCT

1. Cord blood transplantation
What are the results for CB transplantation in acquired SAA?

Unrelated Cord Blood Transplantation for Severe Aplastic Anemia


(n=31)

Influence of Nucleated Cell Dose on Overall Survival of Unrelated Cord Blood Transplantation for Patients with Severe Acquired Aplastic Anemia: A Study by Eurocord and the Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation


(n=71)

Yoshimi et al, BBMT 2008; Peffault de Latour et al, BBMT 2011; 17: 78
Patients from January 1996 to January 2009

<table>
<thead>
<tr>
<th>Patients</th>
<th>71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years</td>
<td>13 (2-68)</td>
</tr>
<tr>
<td>Children (&lt;18 years), n(%)</td>
<td>43 (61)</td>
</tr>
<tr>
<td>Weight, median Kg</td>
<td>47 (9-100)</td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>38/33</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>35 (8-83)</td>
</tr>
</tbody>
</table>

Participating centers, n=32 (23 EBMT)
### Patients-2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAA or vSAA</td>
<td>62 (87%)</td>
</tr>
<tr>
<td>AA-PNH syndrome</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>RIC (Fludarabine-based)</td>
<td>48 (68%)</td>
</tr>
<tr>
<td>ATG</td>
<td>53 (79%)</td>
</tr>
<tr>
<td>Interval diagnosis - CBT (months)</td>
<td>14 (2-140)</td>
</tr>
<tr>
<td>&gt;20 RBC</td>
<td>35 (56%)</td>
</tr>
<tr>
<td>&gt;20 platelets transfusions</td>
<td>42 (67%)</td>
</tr>
</tbody>
</table>

Peffault de Latour et al, BBMT 2010
Results

Neutrophil recovery
37/71 (52% at d+25)

Overall survival
3-year OS: 38% ± 6%

Cell dose > 4x10^7/Kg

- Low rate of GVHD
- 9 myeloablative conditioning…9 deaths!

Peffault de Latour et al, BBMT 2011; 17: 78
French, EBMT adopted protocol

Conditioning regimen:
- Fludarabine 120mg/m²
- Cyclophos 120mg/Kg
- ATG 5 mg/Kg
- TBI 2 Gy

**APCORD (SFGM-TC)**

- UCB #1
- UCB #2

4-6/6 HLA-match UCB
TNC: 4 x 10⁷/kg

Anti CD20: 150mg/m² (D5)
G-CSF (D5)
## Recent studies of cord HSCT for SAA

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Median age (range) yrs.</th>
<th>Conditioning regimen</th>
<th>Engraftment (neutrophils and platelets)</th>
<th>Acute GvHD (Gd II-IV) Chronic GVHD (Cumulative incidence)</th>
<th>Overall survival (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delatour 2011</td>
<td>71</td>
<td>13 (2-68)</td>
<td>RIC (Flu-based) 68%</td>
<td>Median time for NE 25 days and PE 45 days</td>
<td>aGVHD 20±5% cGVHD 18±5%</td>
<td>3 yr. OS 38±6%</td>
</tr>
<tr>
<td></td>
<td>Single=57 Double=14</td>
<td></td>
<td>Myeloablative 31%</td>
<td>CI of neutrophil recovery 51±6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>platelet recovery 37±7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshimi 2008</td>
<td>31</td>
<td>28 (1-72)</td>
<td>TBI +Mel+Flu (n=12)</td>
<td>Median time for NE 19 days and PE 59 days</td>
<td>aGVHD 17% cGVHD 20%</td>
<td>2 yr. OS 41% (6-33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBI +CY+Flu (n=5)</td>
<td>CI of neutrophil recovery 55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBI+Cy+ATG (n=3)</td>
<td>platelet recovery 72%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Others (n=11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamamoto, 2011</td>
<td>12</td>
<td>49 (20-70)</td>
<td>RIC Flu+Mel+TBI(4Gy)</td>
<td>Median time for NE 18 days and PE 42 days</td>
<td>aGVHD 5/11 (all Gd 2) cGVHD 3/9 (all limited)</td>
<td>3 yr. OS 83%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11/12 engrafted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu, 2012</td>
<td>18</td>
<td>17 (5-61)</td>
<td>RIC Flu+CY+ATG</td>
<td>Median time for NE 37 days and PE 87 days</td>
<td>None reported</td>
<td>2 yr. OS 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/16 engrafted</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RIC=reduced intensity conditioning; Flu=fludarabine; CY=cyclophosphamide; TBI=total body irradiation; ATG=anti thymocyte globulin; NE=neutrophil engraftment; PE=platelet engraftment; CI=cumulative incidence

Unrelated cord transplants for acquired SAA

- Engraftment is a major issue
- Cell dose recommended > $4 \times 10^7$ TNC/kg. Use a double cord if necessary
- Use ≥ 4/6 Ag matched cord units
- Screen for HLA antibodies that may be directed against the cord unit(s)
- Myeloablative conditioning not recommended
- Consider using the current EBMT SAA protocol
Haploidentical HSCT for SAA?

Attractions
• Graft is available for > 95% patients
• Time to procure graft is short
• Cost is low compared to cord blood unit(s)

But...
• Recipient HLA antibody(ies) directed against donor precludes use of that donor
• Published data indicates poor outcomes
• High risk GVHD and graft failure, immune deficiency
What is the data for Haplo transplants in SAA?

<table>
<thead>
<tr>
<th>Study Description</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated peripheral blood stem cell transplantation with ‘megadoses’ of purified CD34+ cells in three children with refractory severe aplastic anemia</td>
<td>3</td>
</tr>
<tr>
<td>Haploidentical transplants</td>
<td>3</td>
</tr>
<tr>
<td>Success</td>
<td>1</td>
</tr>
<tr>
<td>Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases</td>
<td>3</td>
</tr>
</tbody>
</table>

RA Brodsky, L Luznik, J Bolaños-Meade, MS Leffell, RJ Jones and EJ Hersh.
A survey of fully haploidentical hematopoietic stem cell transplantation in patients with severe aplastic anemia

A study by the Severe Aplastic Anemia Working Party (SAAWP) and Paediatric Diseases Working Party (PDWP) of the European Blood and Marrow Transplantation Group (EBMT)

Ciceri et al. Bone Marrow Transplant 2013; 48:183
# Patient details

73 pts, transplanted 1976-2011

<table>
<thead>
<tr>
<th>Age</th>
<th>At diagnosis</th>
<th>At haplo SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>9.8 (2.5-69)</td>
<td>12 (2.5-70)</td>
</tr>
<tr>
<td>&lt;12y</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>&gt;12 - 18</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>&gt;18</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

**Haplo**

1\(^{\text{st}}\) transplant 59 pts (7 received a 2\(^{\text{nd}}\) haplo as rescue)

- 2\(^{\text{nd}}\) transplant 12 pts
- 3\(^{\text{rd}}\) transplant 1 pts (+1 rescue)
- 4\(^{\text{th}}\) transplant 1 pts (+1 rescue)

Conditioning: myeloablative in 42%. TBI 19%, ex vivo manipulation 53%

Median time from diagnosis to transplant 324 days (10 – 5373)
Overall survival

Hence, a new approach is needed .........
Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases

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Summary

• Major improvements in HSCT have resulted in changes in indications; a main goal is elimination of chronic GVHD (and graft rejection)
• Alternative donor HSCT needs to be improved; for selected patients, experienced centres, as part of clinical trial
• Current research is aimed at early prediction of lack of response to IST and molecular analyses for diagnosis of constitutional BMF and other myeloid disorders